

Neurogenic Changes

Denervation • Reinnervation • Morphologic interpretation

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Learning outcomes

Relate a motor unit to the histochemical fiber-type pattern.

Explain denervation atrophy, reinnervation and motor-unit enlargement.

Differentiate fiber-type grouping from grouped atrophy.

Interpret these changes in acquired neurogenic disease and spinal muscular atrophy.

Two routes to skeletal muscle weakness

Neurogenic injury: Loss or disruption of the innervating motor neuron/axon.

Neurogenic

 **Motor neuron / axon**

Loss of effective innervation

Myopathic

 **Muscle fiber**

Primary myofiber injury

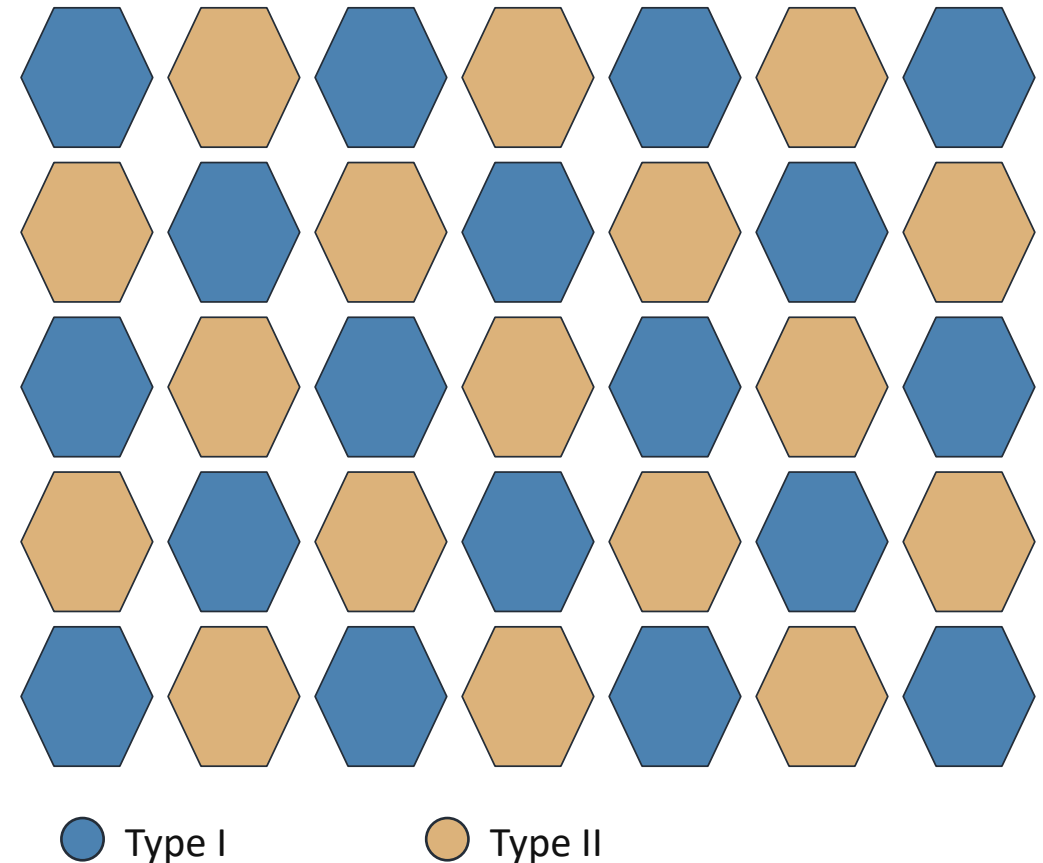
Two injury compartments; Morphology provides localization clues

Adult skeletal muscle: Organizational baseline

Multinucleated myofibers assemble into fascicles.

Fiber phenotype differs among myofibers within one fascicle.

Recognition of abnormal patterns requires a normal reference.



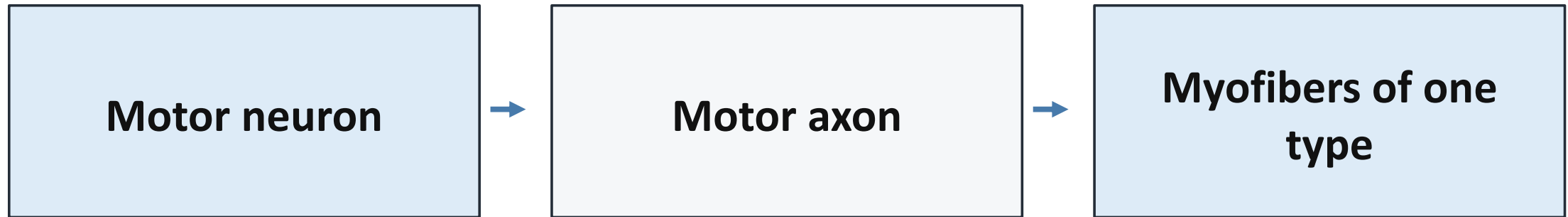
Schematic — not histologic evidence

A motor unit is a functional ensemble

One motor neuron and its axon form the neural component.

All skeletal myofibers supplied by that neuron belong to its motor unit.

Motor-unit composition explains the spatial effects of axonal loss.



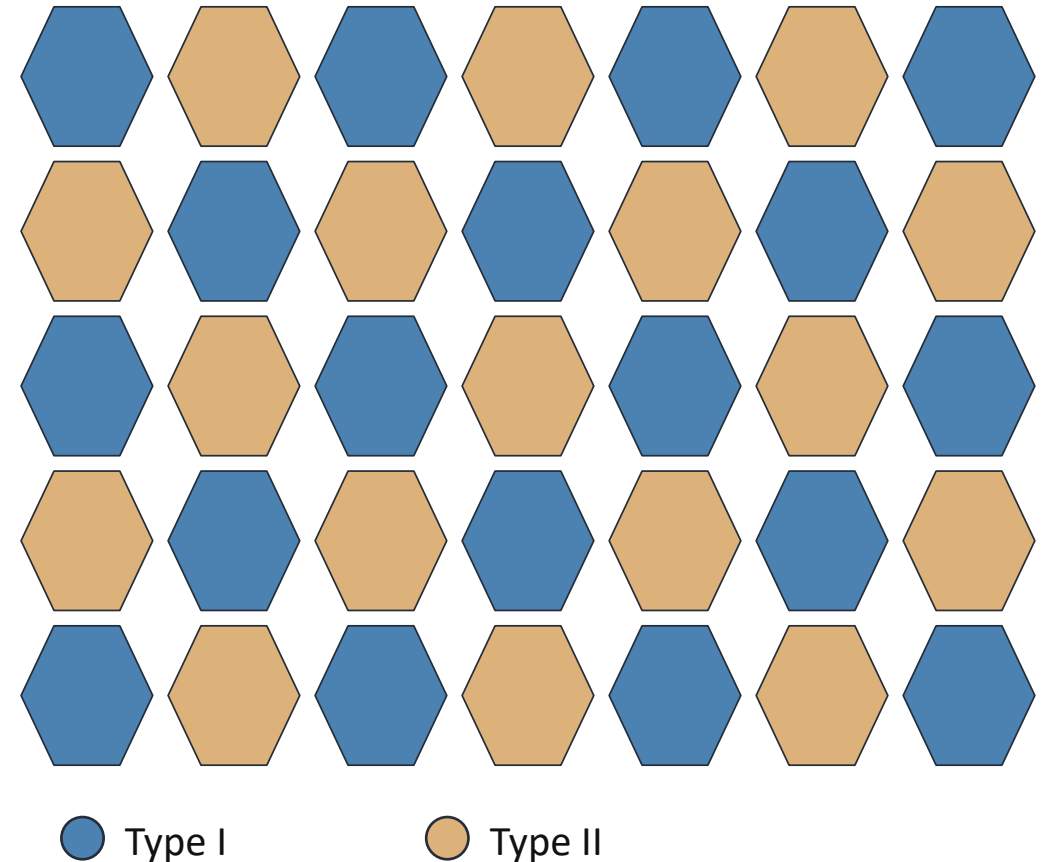
Schematic causal sequence

Fiber type is specified by motor innervation

Myofibers of a single motor unit share the same fiber type.

Different motor units supply intermingled fibers in normal muscle.

Changing innervation may change the phenotype of a rescued fiber.



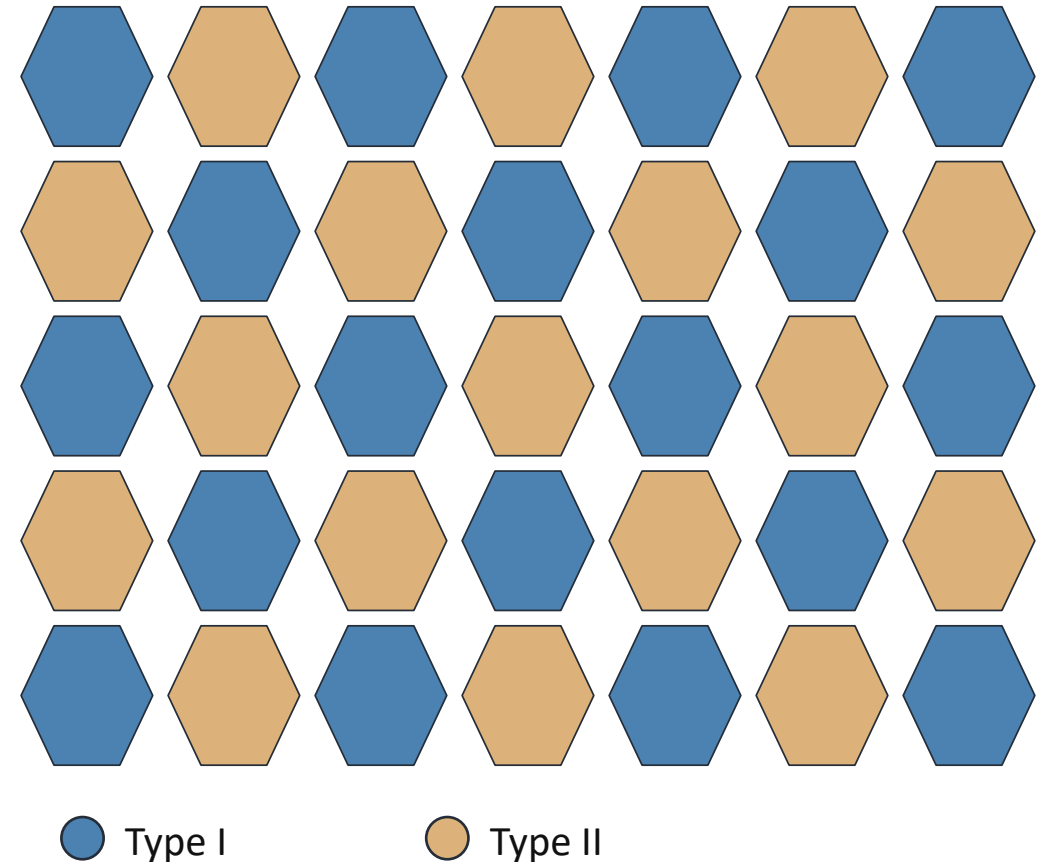
Schematic — not histologic evidence

Normal muscle displays a checkerboard pattern

Type I and type II fibers are admixed rather than segregated.

Alternating histochemical staining reflects mixed motor-unit territories.

Large same-type territories suggest prior reinnervation.



Schematic — not histologic evidence

Type I fibers: Endurance-oriented phenotype

Type I fibers support sustained force and aerobic activity.

Type I

Sustained force / aerobic

High oxidative capacity

Type II

Fast movement

High glycolytic capacity

Higher lipid content and myoglobin are associated with a red appearance.

Type II fibers: Rapid force phenotype

Type II fibers support fast movement and high power.

Type II

High power / fast activity

Relatively fatigable

Type I

Sustained force

More fatigue resistant

Relative mitochondrial and lipid content are lower than in type I.

Functional differences between fiber types

Feature	Type I	Type II
Action	Sustained force	Fast movement
Power & fatigue	Low power; fatigue resistant	High power; fatigues earlier
Metabolism	Oxidative dominant	Glycolytic dominant
Substrate tendency	Lipid rich; glycogen lower	Lipid lower; glycogen rich

Editable comparison; Textbook-derived categories

Muscle histochemistry: Enzyme contrasts

Feature	Type I	Type II
NADH-TR	NADH-TR: dark	NADH-TR: light
ATPase (pH 4.3)	ATPase pH 4.3: dark	ATPase pH 4.3: light
ATPase (pH 9.4)	ATPase pH 9.4: light	ATPase pH 9.4: dark

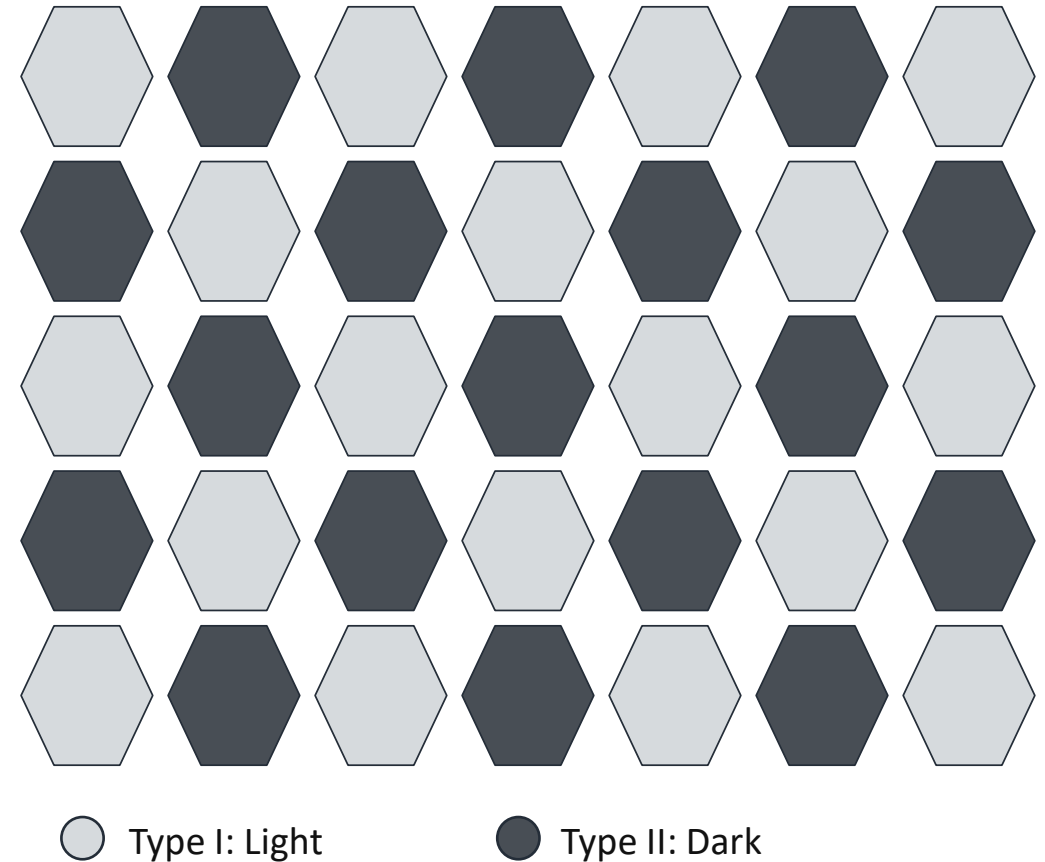
Editable comparison; Textbook-derived categories

ATPase pH 9.4: The polarity of staining

Type I fibers stain light.

Type II fibers stain dark.

In a normal cross-section, the two signals form a mosaic.



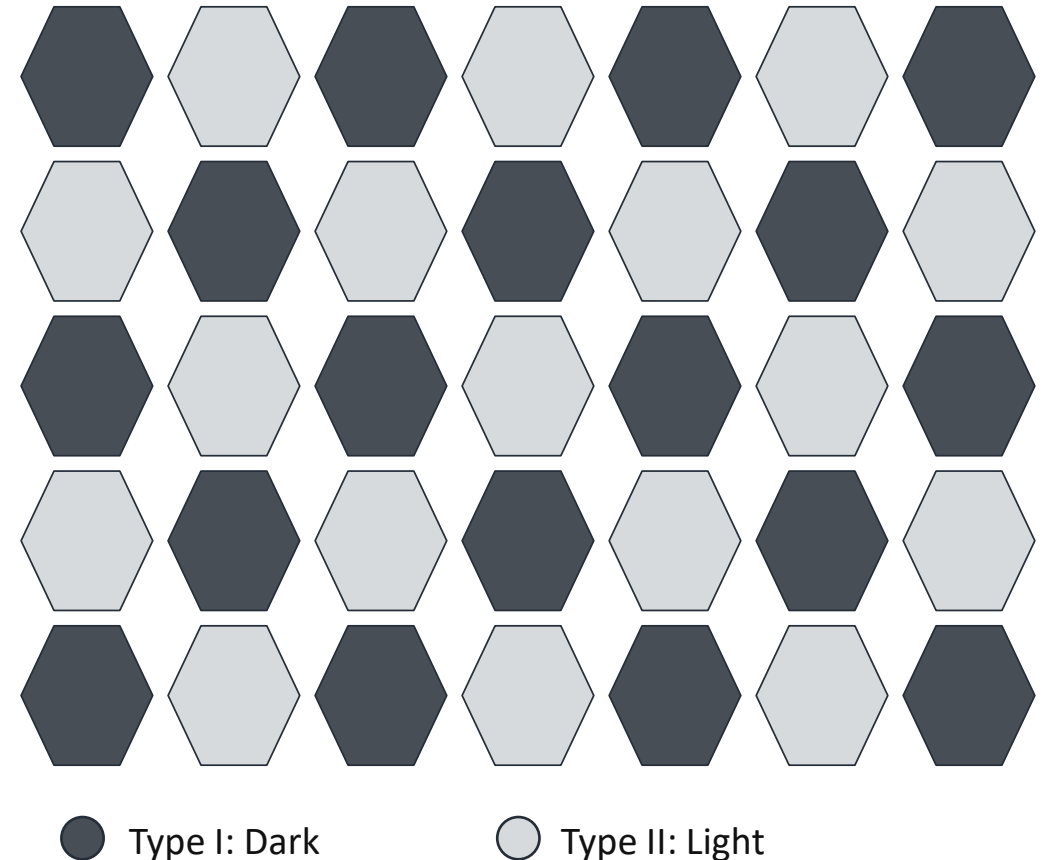
Schematic — not histologic evidence

ATPase pH 4.3: Reverse staining contrast

Type I fibers stain dark at pH 4.3.

Type II fibers stain light at pH 4.3.

A change in stain polarity does not change biological fiber identity.



Schematic — not histologic evidence

NADH-TR: Oxidative enzyme readout

Type I fibers have dark NADH-TR staining.

NADH-TR

Type I: Dark

High oxidative activity

NADH-TR

Type II: Light

Lower oxidative activity

Read the reaction in the context of fiber-type biology.

Fiber type and biopsy pattern: An interpretive chain

Motor neuron identity regulates fiber phenotype.

Motor units ordinarily form a dispersed mosaic.

Loss and replacement of innervation reorganize that mosaic.



Schematic causal sequence

Denervation begins with interruption of input

An axon or its motor neuron is damaged or lost.

Its dependent muscle fibers lose normal innervation.

Affected fibers subsequently diminish in size.

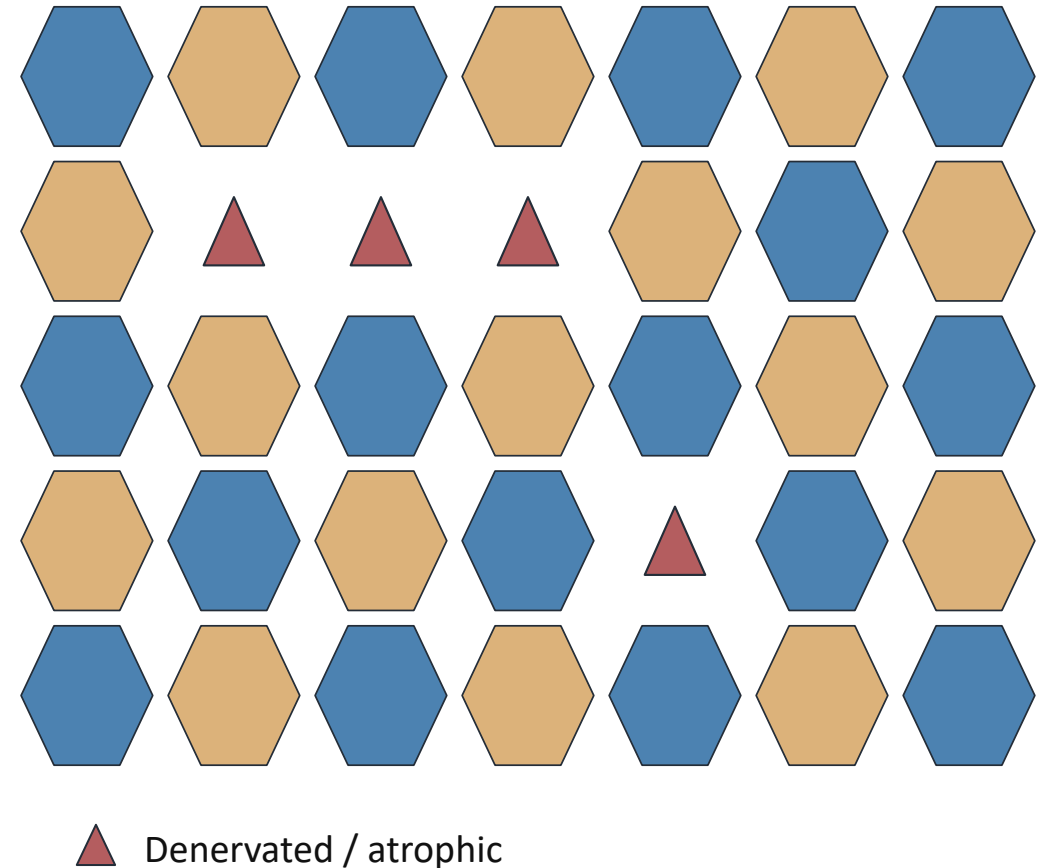


The immediate morphologic consequence is atrophy

Denervated fibers become smaller in cross-section.

The surrounding unaffected fibers may remain relatively preserved.

Distribution of the atrophic cells is more informative than size alone.



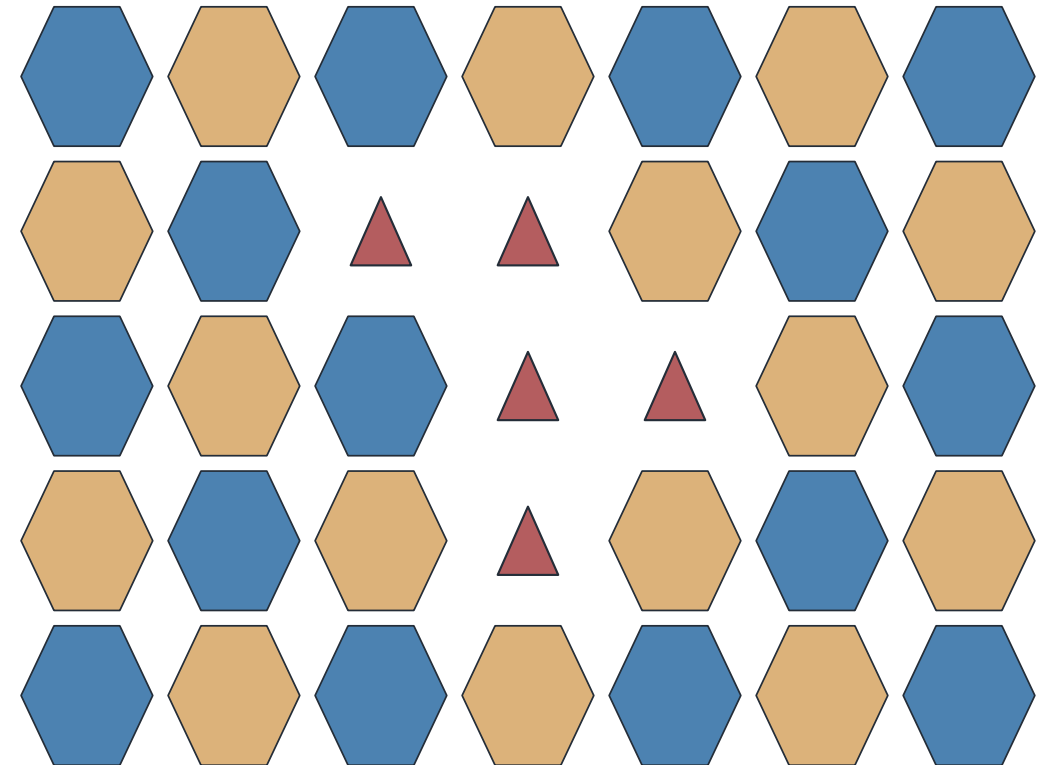
Schematic — not histologic evidence

Denervated fibers may become angulated

The outline often becomes flattened or sharply angulated.

Small angular profiles contrast with normal polygonal/rounded profiles.

This shape is characteristic, not an exclusive diagnostic criterion.



▲ Denervated / atrophic

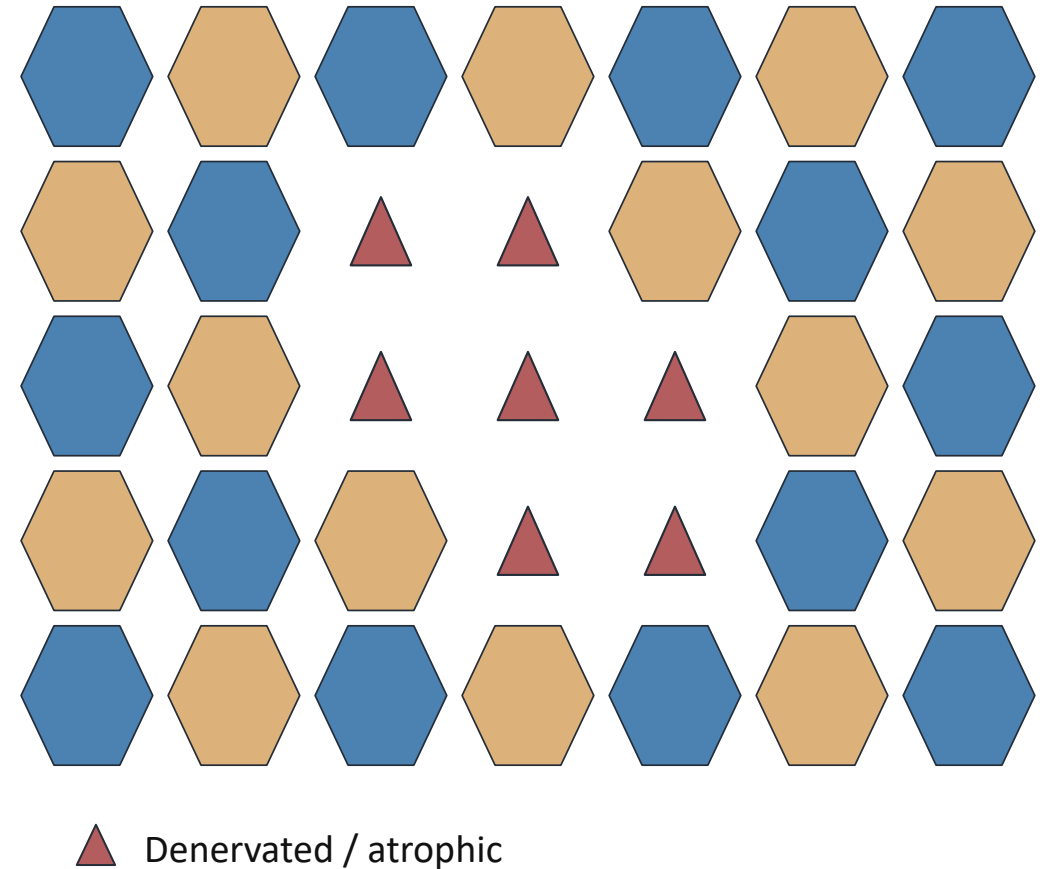
Schematic — not histologic evidence

Why grouped atrophy forms

A single lost motor axon can denervate multiple myofibers.

These fibers may appear as clusters of small, angular profiles.

The grouping is a clue to a shared neural dependence.



Schematic — not histologic evidence

Scattered atrophy versus grouped atrophy

A smaller isolated fiber is a nonspecific observation.

Isolated small profiles

Atrophy alone

Requires context

Clustered small profiles

Group atrophy

Consider denervation

Pattern recognition should integrate shape, distribution and context.

The denervation sequence

Motor neuron/axon damage precedes loss of innervation.

Loss of input precedes reduced myofiber caliber.

Small angular fibers may eventually appear in groups.



Atrophy is a shared endpoint, not a diagnosis

Denervation is one cause of decreased muscle mass.

Neurogenic pattern

 **Fiber groups**

Denervation-associated

Other atrophy

 **Several etiologies**

Disuse / steroids / cachexia

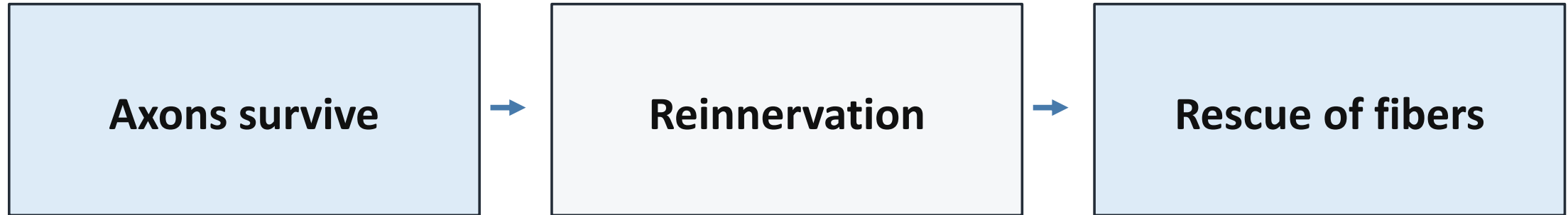
Two injury compartments; Morphology provides localization clues

Surviving motor axons can compensate

Denervated myofibers may receive innervation from residual motor axons.

The rescued fiber becomes incorporated into a different motor unit.

This response partially restores the lost neural input.



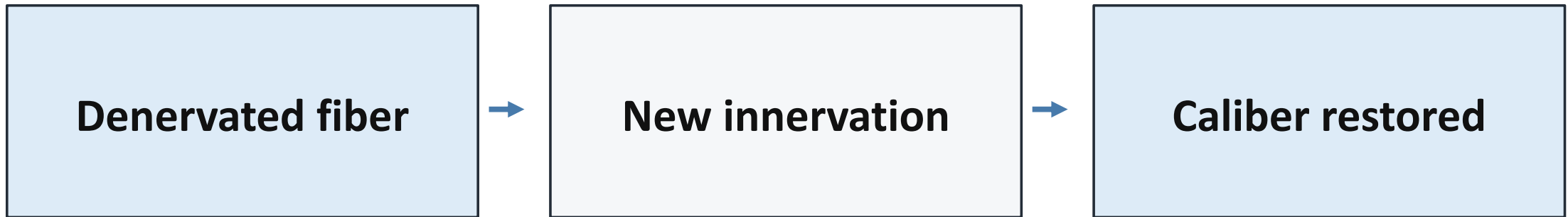
Schematic causal sequence

Reinnervation can restore myofiber caliber

A previously denervated fiber may regain size and shape.

An apparently preserved fiber can therefore have a history of denervation.

Fiber-type architecture helps identify that history.

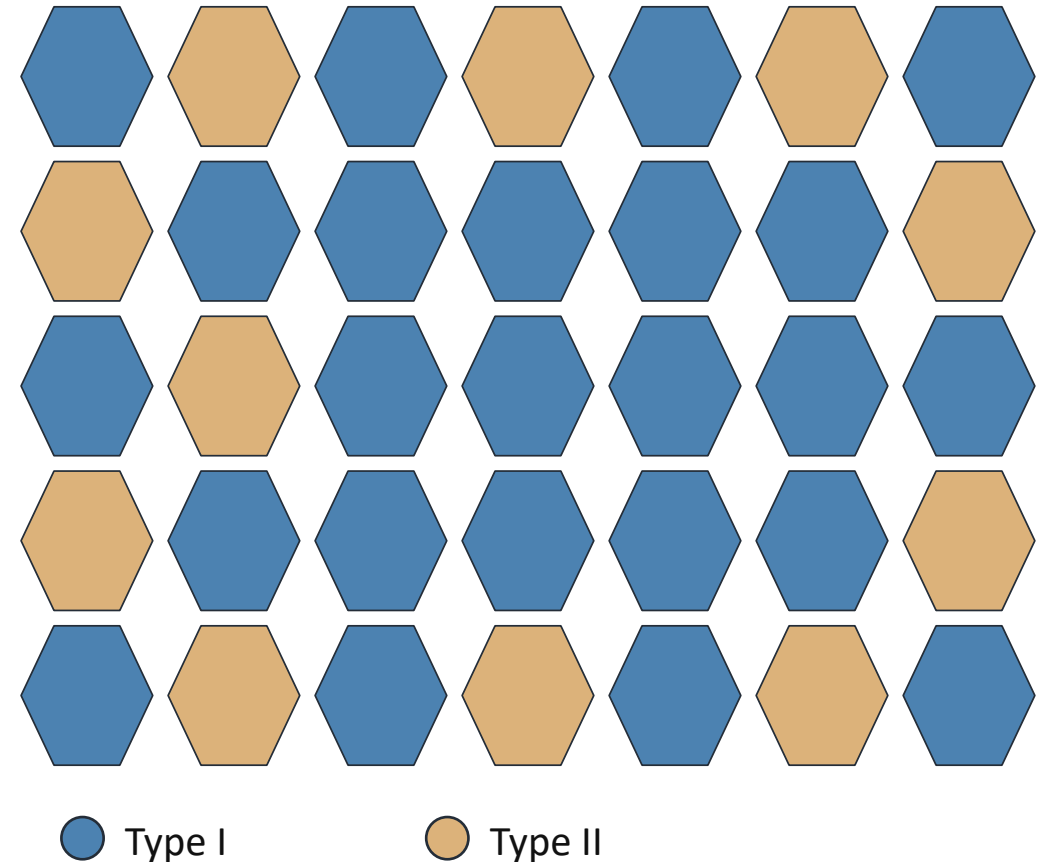


Reinnervation can change fiber identity

The new motor neuron may differ from the original motor neuron.

The reinnervated fiber may switch fiber type.

Nearby myofibers supplied by one surviving axon then share the same type.



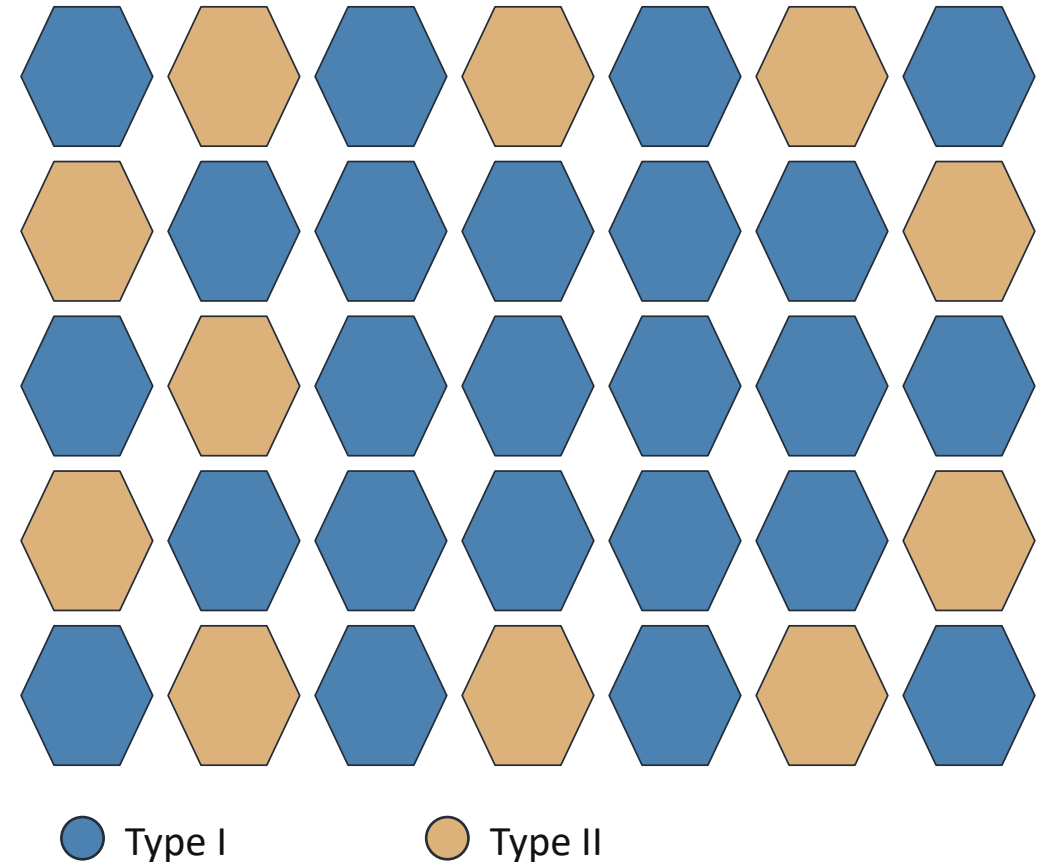
Schematic — not histologic evidence

Fiber-type grouping marks remodeling

Contiguous fibers become predominantly one histochemical type.

The normal checkerboard appearance is diminished locally.

This pattern points to repeated denervation and reinnervation.



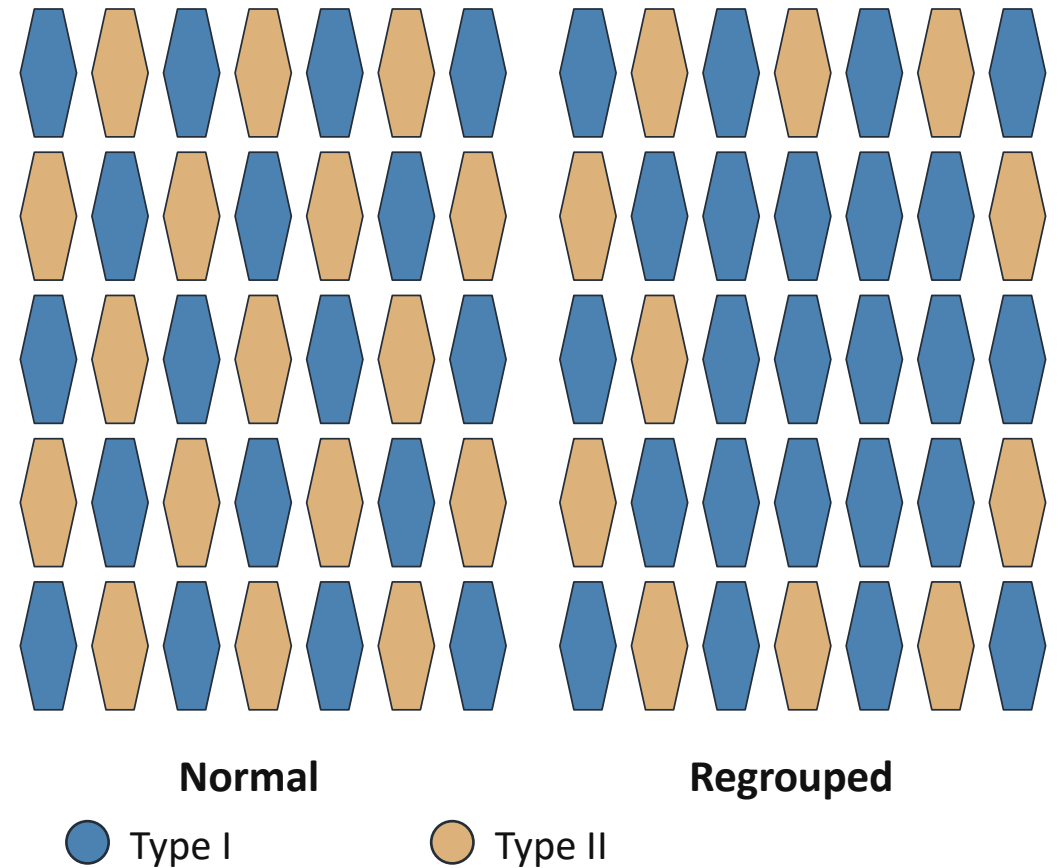
Schematic — not histologic evidence

Normal mosaic versus type grouping

The same total number of fibers can have altered spatial organization.

A change in neighborhood, not necessarily loss of all fibers, is central.

Compare an admixed pattern with a single-type territory.



Schematic — not histologic evidence

Motor units enlarge with ongoing axonal dropout

Residual axons acquire increasing numbers of muscle fibers.

Each enlarged motor unit maintains a common fiber type.

Large single-type territories can accumulate in the biopsy.



Schematic causal sequence

Motor-unit enlargement: Benefit and liability

Benefit: Rescued myofibers regain innervation and caliber.

Compensation

More fibers rescued

Improved muscle innervation

Liability

More fibers per axon

Larger affected territory if lost

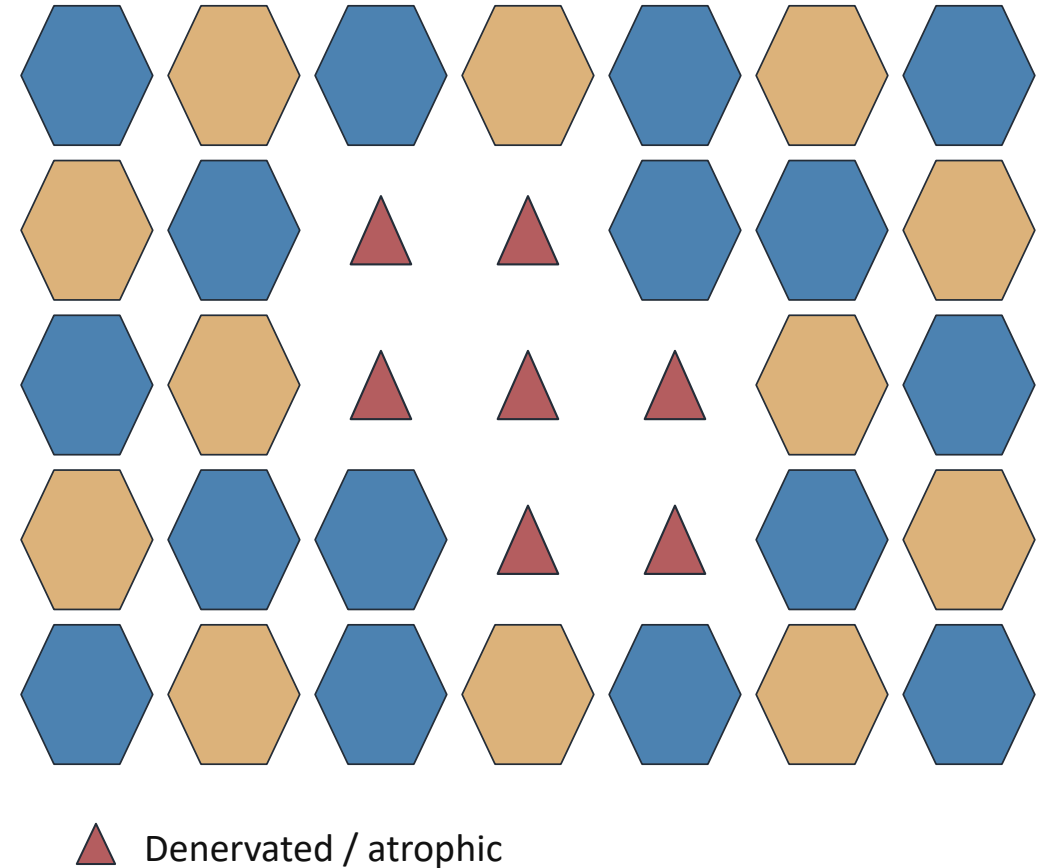
Another axonal injury can affect an unusually large territory.

A remodeled unit can undergo grouped atrophy

A surviving enlarged motor unit is lost later.

The now-denervated same-type territory atrophies together.

Type grouping and grouped atrophy may thus appear sequentially.



Schematic — not histologic evidence

Repeated denervation and reinnervation

Axonal loss induces atrophy.

Reinnervation may restore size while producing fiber-type grouping.

Subsequent axonal loss can generate grouped atrophy in an enlarged unit.



Schematic causal sequence

Two hallmark patterns encode different stages

Grouped atrophy emphasizes current or unresolved denervation.

Type grouping

Fiber phenotype

Historical reinnervation

Grouped atrophy

Fiber size

Loss of innervation

Both can coexist in an evolving neurogenic process.

Reading H&E and fiber-type stains together

Feature	Biopsy finding	Reading
Angulated fibers	Small flattened, angulated fibers	H&E: atrophy / altered shape
Clustered small fibers	Clustered small profiles	H&E: group atrophy
Same-type territories	Contiguous same-type profiles	ATPase: fiber-type grouping
Checkerboard mosaic	Near-alternating fiber types	ATPase: normal-type mosaic

Editable comparison; Textbook-derived categories

The pattern of atrophy helps assign etiology

Feature	Distribution	Association in Robbins
Clusters	Grouped atrophic fibers	Neurogenic process
Fascicle periphery	Perifascicular atrophy	Dermatomyositis
Type II selective	Selective type II fiber atrophy	Steroid exposure or disuse

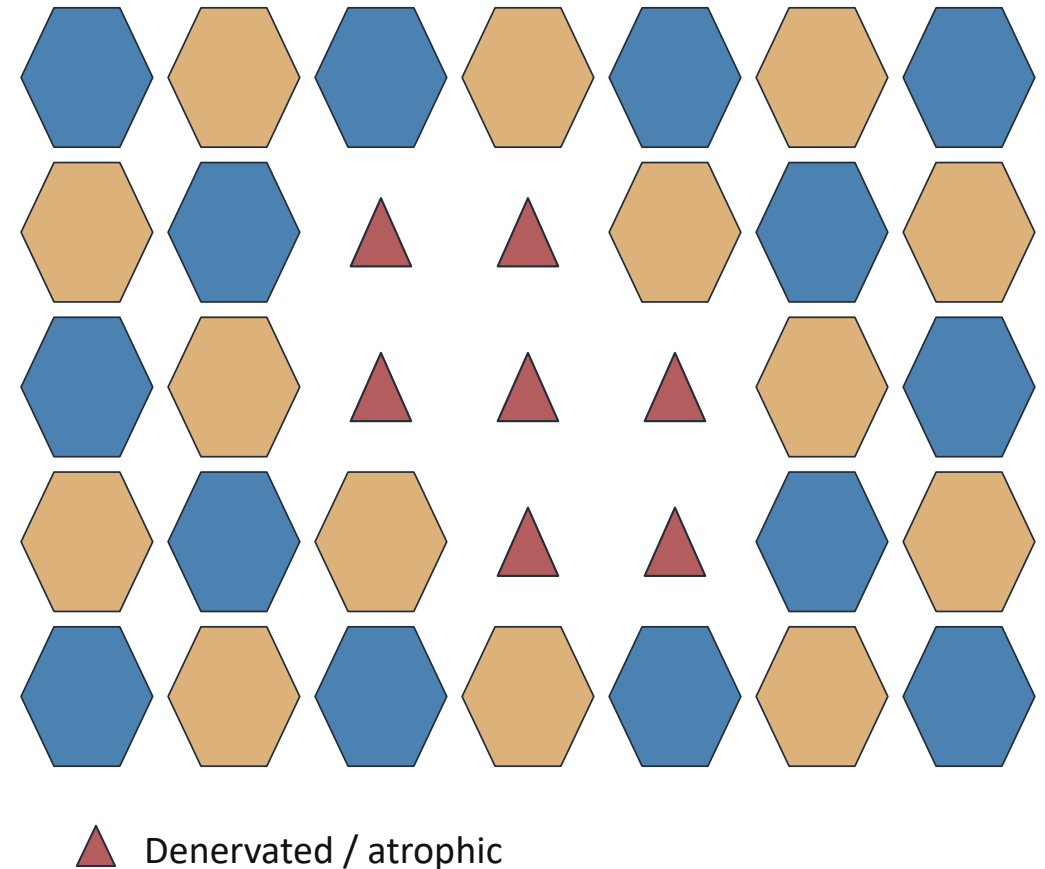
Editable comparison; Textbook-derived categories

Grouped atrophy is spatial clustering

Atrophic fibers are concentrated in a contiguous region.

They may be flattened and angulated.

The group distribution suggests a common motor-unit mechanism.



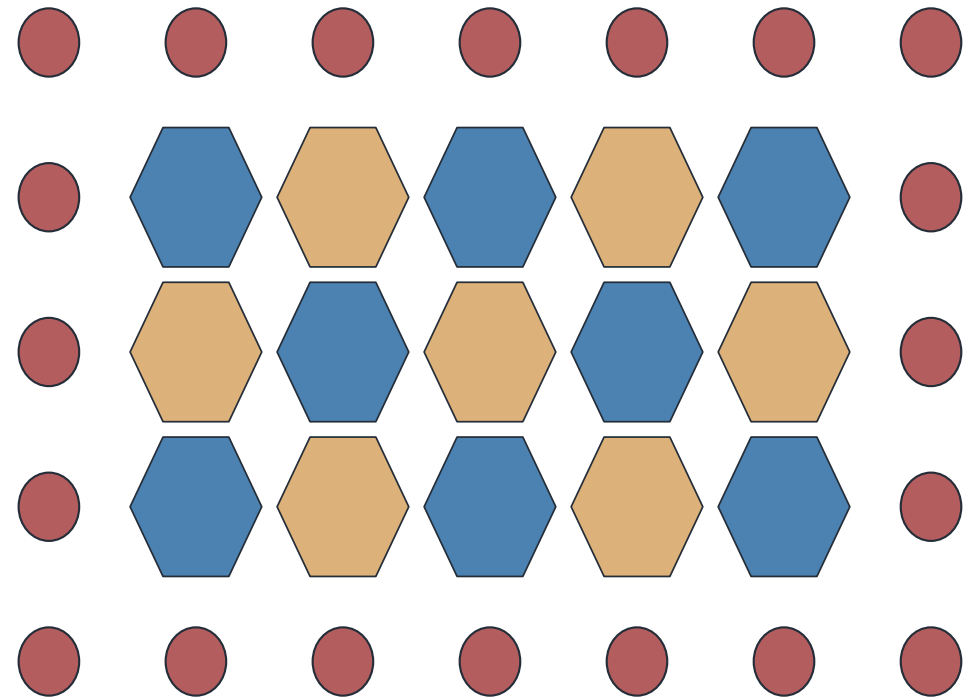
Schematic — not histologic evidence

Perifascicular atrophy is a different geometry

Small fibers preferentially occupy the fascicle edge.

This is the pattern with dermatomyositis.

Do not mistake a peripheral ring for random motor-unit group loss.



▲ Denervated / atrophic

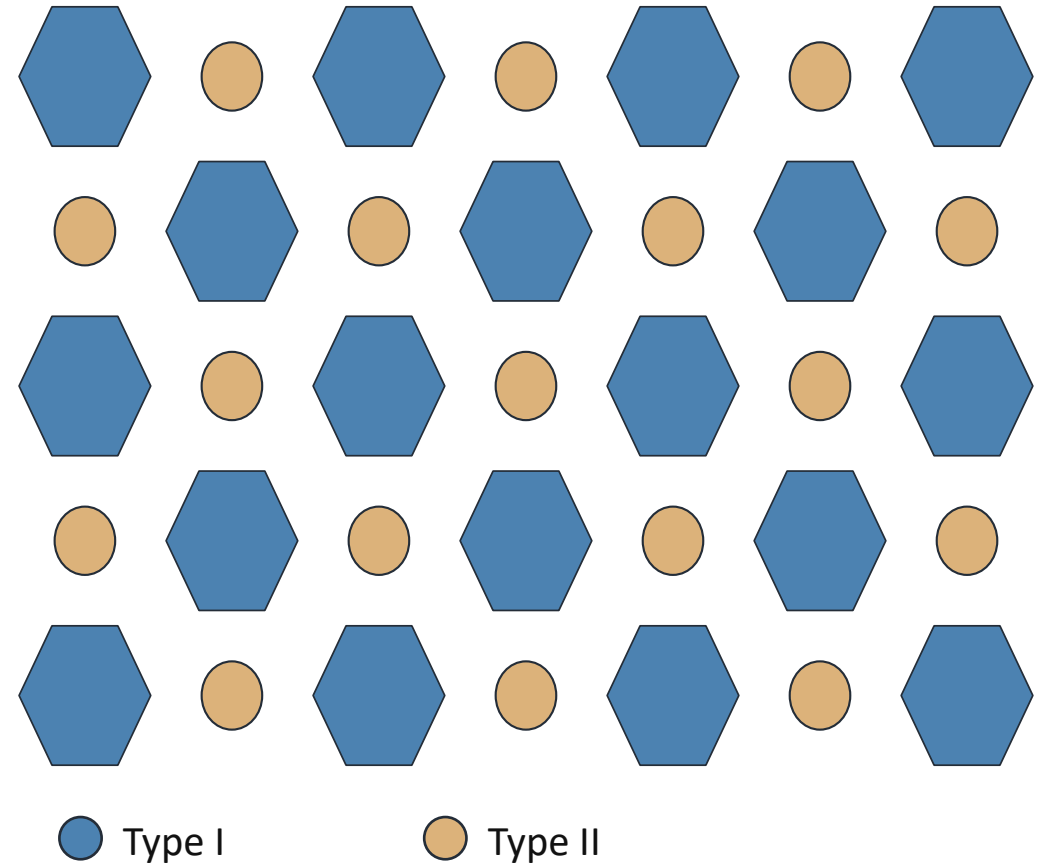
Schematic — not histologic evidence

Selective type II atrophy is different again

Type II fibers are preferentially reduced in size.

Type I fibers are relatively spared.

This with prolonged corticosteroids or disuse.



Schematic — not histologic evidence

Three distinct muscle-atrophy patterns

Feature	Distribution	Association in Robbins
Clusters	Grouped clusters	Neurogenic disease
Fascicle periphery	Perifascicular distribution	Dermatomyositis
Type II selective	Preferential type II small fibers	Disuse or prolonged corticosteroids

Editable comparison; Textbook-derived categories

Neurogenic and myopathic injury differ in origin

Neurogenic: Loss of innervation drives secondary fiber atrophy.

Neurogenic

 **Motor neuron / axon**

Loss of effective innervation

Myopathic

 **Muscle fiber**

Primary myofiber injury

Two injury compartments; Morphology provides localization clues

Primary myopathic injury has a different pathway

Segmental myofiber degeneration may release creatine kinase.

Macrophages clear damaged segments by myophagocytosis.

Activated satellite cells support regeneration of muscle components.



Neurogenic versus myopathic morphologic emphasis

Neurogenic: Angulated/grouped atrophic fibers and type grouping.

Neurogenic

Angulation / groups

Motor-unit mechanism

Myopathic

Degeneration / repair

Primary fiber injury

Some atrophy may occur in both—interpret combined evidence.

Neurogenic atrophy in amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis is an example of a motor-neuron disease producing neurogenic muscle atrophy.

The muscle pathology reflects loss of effective motor innervation.

Muscle biopsy morphology indicates mechanism; ALS requires broader clinical evaluation.

Radiculopathy as a neurogenic cause

Degenerative spine disease can injure a motor nerve root.

Downstream muscle fibers may show denervation-associated atrophy.

The biopsy pattern must be interpreted with anatomic and clinical data.

Peripheral neuropathy as a neurogenic cause

Peripheral axonal injury disrupts motor input to muscle.

Denervation and compensatory reinnervation can reshape muscle architecture.

Muscle biopsy cannot by itself specify which neuropathy is present.

Neurogenic changes span multiple lesion sites

Feature	Lesion site	Illustrative cause
Motor neuron	Motor neuron	Amyotrophic lateral sclerosis
Nerve root	Motor nerve root	Degenerative radiculopathy
Peripheral axon	Peripheral motor axon	Peripheral neuropathy

Editable comparison; Textbook-derived categories

Spinal muscular atrophy: Inherited motor-neuron disease

Spinal muscular atrophy involves loss of motor neurons.

Autosomal recessive disease caused by loss-of-function variants in SMN1.

Loss of motor innervation produces weakness and muscle atrophy.

SMN1 function and motor-neuron maintenance

SMN1 encodes survival motor neuron protein.

The protein participates in spliceosomal functions and ribonucleoprotein biogenesis.

SMN1 deficiency perturbs processes required for motor-neuron homeostasis.

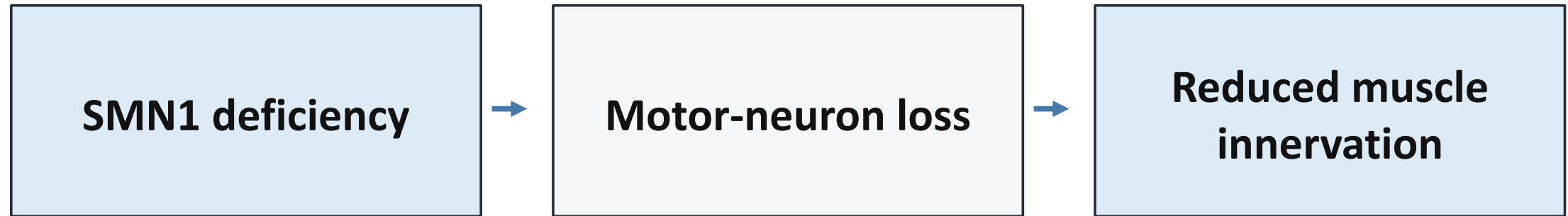


SMN1 deficiency leads to denervation

Deficiency can cause loss of motor neurons.

Loss may begin before birth.

Affected skeletal myofibers may never receive normal initial innervation or become denervated.



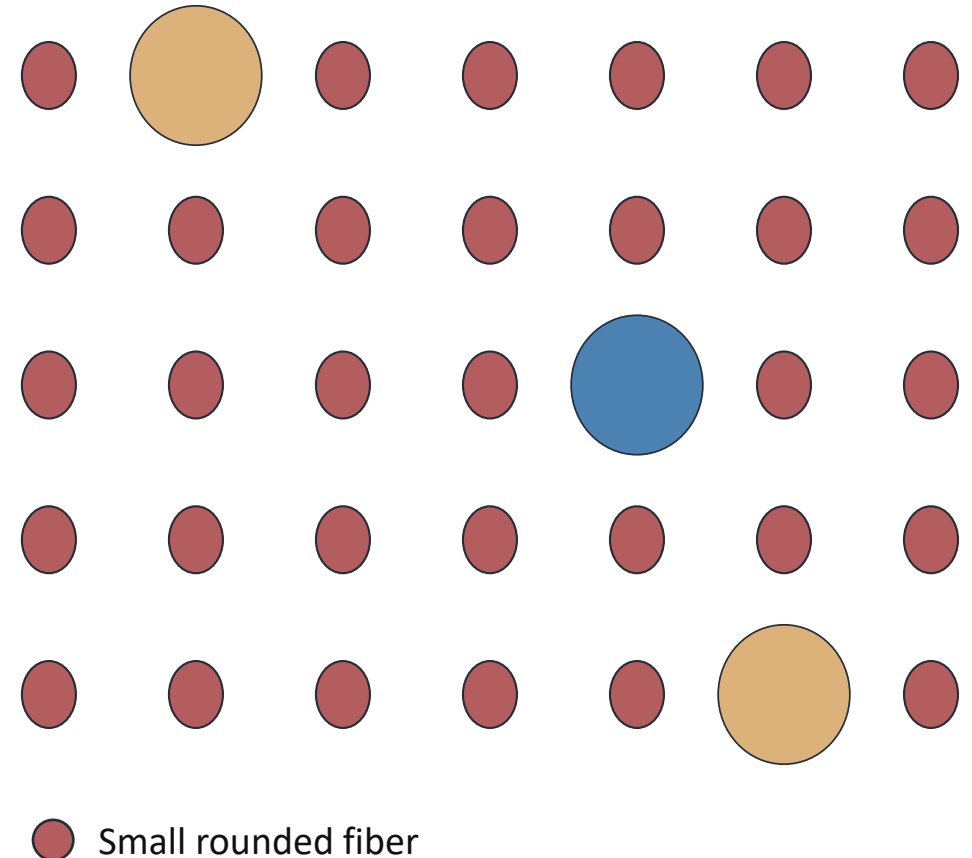
Schematic causal sequence

Severe infantile SMA: The characteristic biopsy picture

Broad zones contain markedly atrophic, rounded fibers.

Scattered fibers are normal-sized or hypertrophied.

The contrast reflects severe motor-neuron loss with residual innervation.



Schematic — not histologic evidence

Rounded atrophic SMA fibers and angular fibers

Severe infantile SMA: Many extremely small, rounded myofibers.

Severe infantile SMA

Small round fibers

Scattered enlarged fibers

Other denervation

Small angulated fibers

Group atrophy possible

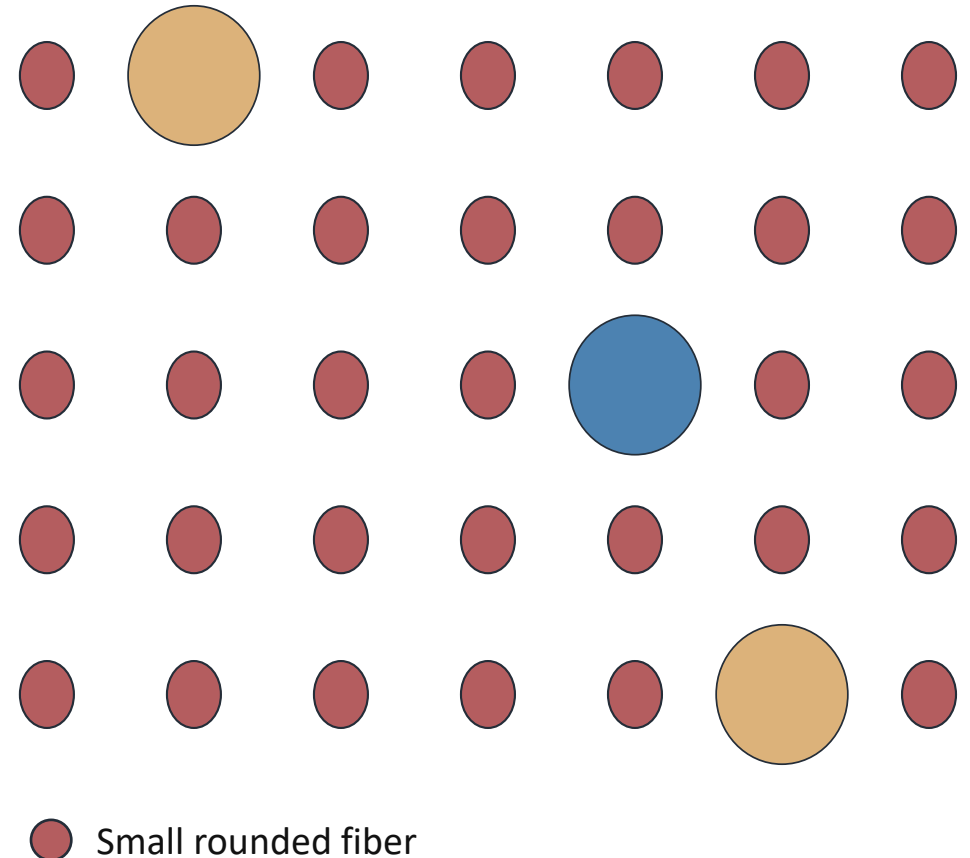
Morphologic pattern varies with disease setting and timing.

Why some SMA fibers remain large

Remaining motor neurons innervate a subset of fibers.

These preserved fibers may develop compensatory hypertrophy.

Thus an SMA biopsy can show striking fiber-size disparity.



Schematic — not histologic evidence

SMA illustrates developmental denervation

SMN1 deficiency may impair initial innervation in utero.

Early SMA

May start in utero

Initial innervation impaired

Acquired axonal injury

Input lost later

Previously innervated fibers

Both processes ultimately yield neurogenic muscle changes.

Interpretation exercise: Clustered angular fibers

Clinical-pathologic scenario (hypothetical)

Grouped angular fibers

An adult with focal limb weakness undergoes muscle biopsy.

Multiple adjacent myofibers are small, flattened and angulated.

What underlying pathophysiologic compartment should be investigated first?

Case interpretation: Favor a neurogenic process

Interpretation

Anatomic localization remains essential

The grouped, angular atrophy points to impaired innervation.

Clinical testing should localize the abnormality to motor neuron, nerve root or peripheral nerve.

Histology alone does not specify the particular cause.

Interpretation exercise: Altered ATPase mosaic

Clinical-pathologic scenario (hypothetical)

Large same-type territories

A biopsy contains broad adjoining territories with one ATPase-defined fiber type.

Fiber caliber is mostly preserved within those territories.

What preceding biological event best explains this organization?

Case interpretation: Reinnervation and switching

Interpretation

A fiber-type map preserves the reinnervation history

The finding represents fiber-type grouping.

Formerly denervated fibers can be reinnervated by a residual axon.

New motor-unit identity can alter the fiber type and restore caliber.

Interpretation exercise: Severe infantile weakness

Clinical-pathologic scenario (hypothetical)

Numerous small rounded fibers

An infant with severe generalized weakness has numerous small rounded fibers.

Rare larger fibers are normal-sized or hypertrophied.

Which source-described inherited motor-neuron disorder fits the morphology?

Case interpretation: Spinal muscular atrophy

Interpretation

Residual innervation produces size disparity

The pattern matches Robbins' description of severe infantile SMA.

SMN1 deficiency causes motor-neuron loss and impaired innervation.

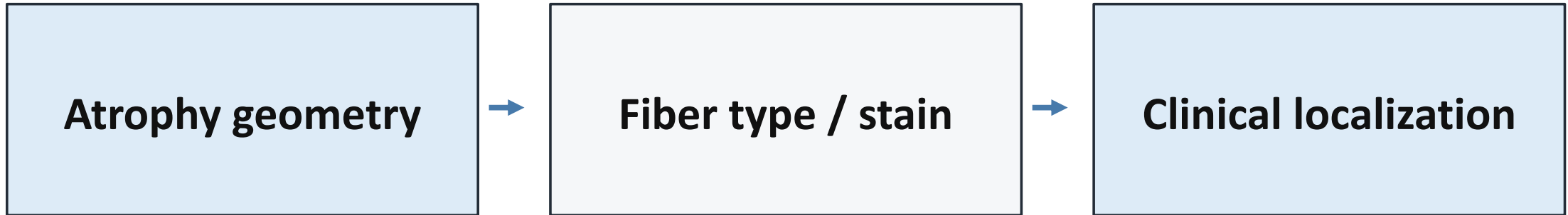
Residual innervated fibers can remain large or become hypertrophic.

A practical morphology-first reading sequence

Identify where the small fibers lie: Grouped, peripheral or type-selective.

Assess fiber shape and whether an enzyme-stain mosaic is preserved.

Combine morphology with clinical localization and cause.



Interpretive pitfalls to avoid

Do not treat every small fiber as proof of denervation.

Do not confuse same-type grouping with grouped atrophy; The former is phenotypic, the latter size-based.

Do not infer ALS, radiculopathy or SMA from a single histologic sign.

Integrated pathology conclusions

Denervation commonly yields small, angulated myofibers.

Compensatory reinnervation can restore caliber and produce fiber-type grouping.

Subsequent loss of enlarged motor units produces grouped atrophy.

Severe infantile SMA can instead show many rounded atrophic fibers with a few hypertrophied survivors.

Primary reading

Robbins, Cotran & Kumar: Pathologic Basis of Disease. 11th ed. (2026).

Chapter 27: Peripheral Nerves and Skeletal Muscles, pp. 1116–1117.

Sections: Skeletal Muscle Atrophy; Neurogenic Changes; Myopathic Changes.

Supporting items: Table 27.2; Figs. 27.7 and 27.8.